# The Pathophysiology and Dangers of Silent Hypoxemia in COVID-19 Lung Injury

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## Abstract

The ongoing coronavirus disease (COVID-19) pandemic has been unprecedented on many levels, not least of which are the challenges in understanding the pathophysiology of these new critically ill patients. One widely reported phenomenon is that of a profoundly hypoxemic patient with minimal to no dyspnea out of proportion to the extent of radiographic abnormality and change in lung compliance. This apparently unique presentation, sometimes called "happy hypoxemia or hypoxia" but better described as "silent hypoxemia," has led to the speculation of underlying pathophysiological differences between COVID-19 lung injury and acute respiratory distress syndrome (ARDS) from other causes. We explore three proposed distinctive features of COVID-19 that likely bear on the genesis of silent hypoxemia, including differences in lung compliance, pulmonary vascular responses to hypoxia, and nervous system sensing and response to hypoxia. In the context of known principles of respiratory physiology and neurobiology, we discuss whether these particular findings are due to direct viral effects or, equally plausible, are within the spectrum of typical ARDS pathophysiology and the wide range of hypoxic ventilatory and pulmonary vascular responses and dyspnea perception in healthy people. Comparisons between lung injury patterns in COVID-19 and other causes of ARDS are clouded by the extent and severity of this pandemic, which may underlie the description of "new" phenotypes, although our ability to confirm these phenotypes by more invasive and longitudinal studies is limited. However, given the uncertainty about anything unique in the pathophysiology of COVID-19 lung injury, there are no compelling pathophysiological reasons at present to support a therapeutic approach for these patients that is different from the proven standards of care in ARDS.

**Keywords:** COVID-19; silent hypoxemia; acute respiratory distress syndrome; SARS-CoV-2

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Coronavirus disease (COVID-19) lung injury manifestations range from minimal symptoms and signs to severe acute respiratory distress syndrome (ARDS) and have led to a wide-ranging discussion about its pathophysiology and differences from ARDS due to other causes (1–4). One observation that has engendered considerable attention and controversy across social media, the nonmedical press (5), and case reports (6–8) is that of "silent hypoxemia." This term denotes marked arterial hypoxemia despite an apparent lack of dyspnea in conscious and alert patients. In some cases, hypoxemia is profound, with reported values of oxygen saturation as measured by pulse oximetry ($Sp_{O_2}$) and arterial oxygen pressure ($Pa_{O_2}$) as low as 70% and 40 mm Hg, respectively (6). The true extent of silent hypoxemia is unknown because there is no consensus definition. The severity of hypoxemia in those without dyspnea is rarely reported and varies widely, although it may affect as many as one-third of patients with COVID-19 lung injury if defined as the absence of dyspnea in patients rapidly developing respiratory failure (1, 2, 4, 9). However, these estimates should not be taken as the true prevalence of silent hypoxemia because they do not provide contemporaneous $O_2$ saturation data and dyspnea scores, and some patients in these series without dyspnea may be those who are not yet hypoxemic.

It is extraordinary that in the half-century since the first description of ARDS,

with which COVID-19 lung injury shares many similarities, silent hypoxemia has never been reported. Most patients with ARDS have dyspnea, but data on rates of dyspnea in comparison with rates of hypoxemia are lacking (10). In severe virally induced ARDS, including ARDS induced by severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and H1N1 influenza, those requiring oxygen without dyspnea ranged from 0% to 27% (11–14), suggesting that silent hypoxemia is virally mediated. In a recent analysis of prehospitalization patients assessed by emergency medical services, the average $Sp_{O_2}$ divided by respiratory rate was 5.0 in March of 2020, compared with 3.2–3.5 in the same month of the preceding 3 years, which is suggestive of more silent hypoxemia in the COVID-19 era (15). However, the magnitude of the pandemic perhaps increases the likelihood that rare manifestations of ARDS, such as silent hypoxemia, will become more readily visible.

This review will focus on mechanisms, either virally induced or within the broad, normal range of hypoxic sensitivity in the lung and nervous system in healthy people, which could lead to profound hypoxemia without apparent dyspnea, based on what is currently known about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and normal respiratory physiology and pathophysiology in other forms of ARDS. We specifically address three aspects: parenchymal compliance, hypoxic pulmonary vascular regulation, and the neurobiology of ventilatory control and dyspnea sensation. All are inextricably linked to the phenomenon of silent hypoxemia. Table 1 highlights the proposed mechanisms and features of each and what is known of their salient contributors in COVID-19 and ARDS. We describe what theories have been proposed and include supporting or refuting data from observations of COVID-19 lung injury and non–COVID-19 ARDS. Lastly, we highlight how future studies might bring further insight and perspective to the phenomenon.

## Pathogenesis of COVID-19 Lung Injury

It is beyond the scope of this review to fully describe the pathogenesis of new lung injury, but a brief overview is useful for providing the background of the physiological

questions discussed. The prevailing paradigm supposes that the initial insult (via direct viral infection and/or secondary immune system–mediated inflammation) leads to alveolar epithelial and capillary endothelial damage with interstitial edema and alveolar fluid filling. Autopsy data reflecting advanced disease reveal the typical features of ARDS, including exudative and proliferative phases of diffuse alveolar damage, hyaline membranes, edema, atypical pneumocyte hyperplasia, alveolar hemorrhage, infarction, endothelial-cell injury, and capillary congestion with microthrombosis and dilation (16, 17). Possibly somewhat more pronounced in COVID-19 than in ARDS is a greater extent of vascular abnormalities, including macrothrombosis and microthrombosis, endothelial-cell injury, vascular dilation, and aberrant angiogenesis (16, 18–21). These vascular findings, also occurring in many other organs, have led to the idea that COVID-19 lung injury is part of a broader systemic vascular pathology differing from that of ARDS (22).

## Lung Parenchyma, Compliance, and Hypoxemia in COVID-19 Lung Injury

In early descriptions of critically ill hypoxemic patients with COVID-19 (23, 24), roughly 20% had "normal to near normal" static total respiratory system compliance ($C_{ST}$) of 70–90 ml/cmH$_2$O, with an average of 50 ml/cmH$_2$O. Neither of these two small studies reported any correlation of $C_{ST}$ with pulmonary radiological abnormalities. On the basis of these observations, Gattinoni and colleagues (25) proposed a controversial high-compliance phenotype (termed "L type" for low elastance, low recruitability with positive end-expiratory pressure [PEEP], and greater perfusion to regions of low alveolar volume [$V_A$] in relation to cardiac output [$\dot{Q}$] rather than shunt formation) combined with vasoplegia (i.e., the absence of hypoxic pulmonary vasoconstriction [HPV]) as a partial explanation for silent hypoxemia.

### Reasons/Evidence for Possible Uniquely Better Compliance in COVID-19 Lung Injury
Two explanations have been advanced to explain higher compliance early in COVID-19 lung injury with severe hypoxemia. The first is the focality and limited extent of lung injury on computed tomography (CT) images

(often peripheral and basilar ground-glass opacities [GGOs]) in many patients early in the disease course (26). GGOs occur in viral pneumonias and with numerous processes, including incomplete alveolar filling and collapse, increased blood volume and perfusion, and expansion of the interstitial space, all of which only partially reduce aeration and ventilation of these regions with a lesser impact on elastic recoil. Because the work of breathing increases with greater elastic recoil, those with less lung involvement may have relatively higher compliances and thus have less dyspnea. A second explanation is that the gas exchange abnormalities arise primarily from a vascularly mediated injury, leading to low Alveolar ventilation–perfusion ratio ($\dot{V}_A/\dot{Q}$) rather than to shunt creation and leading to less reduction in aeration and lung density (23). A vascular etiology for GGOs would be consistent with the high prevalence of hypercoagulability and with the extensive *in situ* pulmonary microthrombosis, microembolism, and endothelialitis at autopsy (16, 20). Two observations, however, vitiate this argument. First, lung biopsy specimens taken from patients with early COVID-19 (27–29) do not show the vascular pathologies noted in autopsies. Second, contrary to the belief that nonperfused lung regions retain normal compliance, high $\dot{V}_A/\dot{Q}$ or dead space units become stiffer, a phenomenon termed "hypocapnic pneumoconstriction," which is followed by a cessation of surfactant production (30). Hypoxemia associated with high $\dot{V}_A/\dot{Q}$–unit creation is due to blood diverted to other lung units that cannot increase ventilation sufficiently and thus themselves become low $\dot{V}_A/\dot{Q}$ regions. Furthermore, a greater presence of high $\dot{V}_A/\dot{Q}$ regions as a supporting reason for higher compliance is based solely on the $CO_2$ dead space calculated by the Bohr-Enghoff equation. This equation not only measures the attributable dead space from anatomic and high $\dot{V}_A/\dot{Q}$ regions but also equally measures areas of low $\dot{V}_A/\dot{Q}$ and shunt, as clarified using the multiple inert gas elimination technique (MIGET) (31).

### Reasons and Evidence against a Uniquely Better Compliance in COVID-19 Lung Injury
Although a few groups have reported a higher-compliance phenotype in COVID-19 lung injury as compared with ARDS, in subsequent studies comprising hundreds of patients (2, 4), the average $C_{ST}$ was low (<35 ml/cmH$_2$O) even on the first day

**Table 1.** Purported mechanistic explanations for silent hypoxemia and associated reported findings in COVID-19 lung injury and non–COVID-19 ARDS

| | COVID-19 Lung Injury | Non–COVID-19 ARDS |
|---|---|---|
| **Vascular regulation** | | |
| Proposed | Vasoplegia and HPV impaired | Intact vascular responsiveness |
| Observed | • Vascular imaging demonstrates vascular engorgement and increased perfusion in areas of diseased lung (21, 26)<br>• Lung vasculature expresses angiotensin-converting enzyme 2 (52)<br>• Benefit from almitrine and inhaled pulmonary vasodilators argues against global vasoplegia (59, 77)<br>• Mildly elevated PA pressure, by echocardiography and PA catheterization (44–46)<br>• No direct evidence of HPV impairment | • Hypoxemia in ARDS is responsive to almitrine, inhaled pulmonary vasodilators; worsened by systemic vasodilators (57, 58)<br>• Mildly elevated PA pressure and PVR, by PA catheterization (47, 48)<br>• Direct evidence of HPV responsiveness (54) |
| Conclusion | Very limited data with a need for more investigation because of angiotensin-converting enzyme 2 expression in the pulmonary endothelium and arterial smooth muscle | |
| **Lung compliance** | | |
| Proposed | Compliance minimally reduced | Compliance greatly reduced |
| Observed | • $C_{ST}$ range, 20–90 ml/cmH$_2$O in newly intubated patients (2, 4, 23, 24) | • $C_{ST}$ range, 10–78 ml/cmH$_2$O (32, 33) |
| Conclusion | Minimal and clinically nonsignificant differences in observed values, especially given the wide range of compliance seen in non–COVID-19 ARDS | |
| **Neural oxygen sensing and dyspnea perception** | | |
| Proposed | Impaired central and peripheral O$_2$ sensing and dyspnea perception secondary to direct viral effects | Preserved O$_2$ sensing at both peripheral and central chemoreceptors and intact dyspnea perception |
| Observed | • Viral access in brain stem and cortex in humans (68)<br>• Viral brain stem access in animals (67)<br>• Carotid body & brain express angiotensin-converting enzyme 2 (65, 66)<br>• 9–34% of patients with no reported dyspnea (1, 2, 4)<br>• No direct HVR testing performed | • 0–27% of patients with no reported dyspnea in SARS and H1N1 influenza ARDS (11–14)<br>• No direct HVR testing performed |
| Conclusion | Very limited data, with a need for more investigation because of angiotensin-converting enzyme 2 expression in the brain and chemoreceptors and documented viral presence in these sites | |

*Definition of abbreviations*: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; $C_{ST}$ = static total respiratory system compliance; HPV = hypoxic pulmonary vasoconstriction; HVR = hypoxic ventilatory response; PA = pulmonary artery; PVR = pulmonary vascular resistance; SARS = severe acute respiratory syndrome.

of mechanical ventilation, and the broad distribution is consistent with that seen in previous studies of ARDS (32–34). Refuting the idea that higher compliance is associated with a lesser extent of radiographic abnormality, a recent study found no correlation between the amount of affected lung at semiquantitative CT assessment and the $C_{ST}$ (35). Two other studies found no correlation between $C_{ST}$ and recruitability as assessed by *1)* disease duration, *2)* Pa$_{O_2}$/fraction of inspired oxygen ratio (F$_{I_{O_2}}$), or *3)* changes in aerated lung volume with increased PEEP (36, 37). Lastly, there appears to be no relationship between $C_{ST}$ and symptom duration (38) or the Pa$_{O_2}$/(F$_{I_{O_2}}$) (39), nor is it a good predictor of lung injury risk, which is similar to what has been found in ARDS (40). Thus, taken together, the evidence for a unique high-compliance phenotype in COVID-19 is not well supported. It has been found to an equal extent in studies of ARDS and may simply represent an earlier stage in the evolution of lung injury.

## Lung Vascular Regulation, Hypoxic Vasoconstriction, and Hypoxemia in COVID-19 Lung Injury

Pulmonary vascular regulation has been postulated to be impaired in patients with COVID-19 to account for a degree of hypoxemia that is out of proportion to the extent of radiographic abnormality and compliance change (23, 41). The five physiological causes of hypoxemia are low inspired oxygen pressure (P$_{I_{O_2}}$), hypoventilation, diffusion limitation, low ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatch, and shunt formation; only the last two are likely to play as significant a role in COVID-19 lung disease as in ARDS. Studies in patients with ARDS using MIGET, which enables distinguishing hypoxemia owing to diffusion limitation from that caused by low $\dot{V}_A/\dot{Q}$ and shunt formation, find no evidence for diffusion limitation (42). No MIGET analysis of $\dot{V}_A/\dot{Q}$ mismatching in

COVID-19 lung injury has yet been performed to assess for diffusion limitation. The key physiological response to minimizing arterial hypoxemia arising from low $\dot{V}_A/\dot{Q}$ and shunt formation is HPV, and its possible impairment in COVID-19 has been hypothesized.

### Reasons and Evidence for a Possible Unique Vascular Behavior in COVID-19 Lung Injury

Impairment in HPV and vasoplegia could play a role in increasing the severity of hypoxemia in COVID-19 lung injury. CT and dual-energy CT perfusion imaging have revealed enlarged vessels and enhanced perfusion, particularly in GGO areas, supporting the idea of dysregulated perfusion (26, 43). Unfortunately, we have few pulmonary hemodynamic data on COVID-19 lung injury. Using transesophageal echocardiography, estimated pulmonary artery (PA) pressures and pulmonary vascular resistance (PVR) were found to be slightly elevated (44, 45), and this has now been corroborated with PA catheterization in 21 mechanically ventilated patients, showing mild pulmonary hypertension (mean PA pressure, 27 mm Hg; PVR, 1.6 Wood units; and $\dot{Q}$, 7.3 L/min) (46). The data are equivalent to those reported for the majority of patients with ARDS (47, 48). Although these studies do not suggest a generalized vasoplegia and/or loss of HPV, the situation is complicated by the likelihood of regional PVR differences, such that contributions of vascular beds with low resistance and a possible lack of HPV are counterbalanced by other areas of higher resistance due to pulmonary embolism or *in situ* thrombosis, which also occurs in ARDS to a high degree (17).

If HPV is blunted or absent in COVID-19, multiple mechanisms could be responsible. Reductions in alveolar carbon dioxide partial pressure ($P_{A_{CO_2}}$) with hyperventilation diminish HPV (49). In an inflammatory state, nitric oxide (NO) production can be increased via cytokine-mediated upregulation of inducible NO synthase activity (50). Another possibility is that SARS-CoV-2 causes changes in mitochondrial proteins and transduction pathways involved in $O_2$ sensing, as has been shown for SARS-CoV-1 in leukocytes (51). If occurring in lung vessels, impaired vasoregulatory responses to oxygen could be hypothesized. Furthermore, because PA

smooth muscle cells express angiotensin-converting enzyme 2 (52), they may be injured and lose hypoxic sensitivity. Finally, virally mediated endothelial-cell injury (16, 18–20) could impair hypoxia sensing by microvascular endothelial cells transduced to PA vascular smooth muscle (53).

### Reasons and Evidence against a Unique Vascular Behavior in COVID-19 Lung Injury

The above macrovascular and microvascular abnormalities identified in COVID-19 have been identified previously in other forms of ARDS to an almost equal extent (17), arguing against a unique vascular phenotype based solely on the degree of pulmonary embolism and/or *in situ* microthrombosis. Although dual-energy CT perfusion scanning shows possible dysregulated perfusion in COVID-19, this has not yet been studied in ARDS to determine whether such dysregulation (possibly of HPV) is a feature of ARDS. HPV in ARDS has not been studied directly by lowering inspired $O_2$ to reduce alveolar $P_{O_2}$, as has been done in healthy persons (49). The only evidence for HPV in ARDS is from patients receiving extracorporeal membrane oxygenation in whom mixed venous $P_{O_2}$ was raised from 47 to 84 mm Hg by increasing extracorporeal blood flow (54). With an elevation of mixed venous $P_{O_2}$ into regions of shunt formation lacking delivery of inspired $O_2$, mean PA pressure decreased, and PVR fell by 25% (54). Systemic drugs that inhibit HPV in healthy persons (pulmonary vasodilators) and enhance HPV (almitrine) respectively worsen and improve gas exchange in ARDS, consistent with effects on HPV (55–58). As in ARDS, almitrine in several studies improved gas exchange in patients with COVID-19 lung injury (59). Vascular responsiveness to these drugs argues against global vasoplegia. Moreover, they also alter PVR in normoxia (55, 60, 61); thus, these drugs are not ideal for evaluating hypoxic vascular responses and do not clearly establish an alteration in HPV in patients with COVID-19.

What may equally explain hypoxemia that is out of proportion to the extent of lung involvement in some patients with either COVID-19 or ARDS from other causes is that these patients may have intrinsically blunted HPV

(i.e., vasoreactivity at the low end of the normally very wide fivefold variation of the strength of this response among healthy persons [49]) and may thus have a relative inability to divert blood flow away from hypoxic lung regions.

### Dyspnea, Control of Ventilation, and Hypoxemia in COVID-19 Lung Injury

Control of ventilation and responses to environmental and physiological drivers of dyspnea are complex (62). Neural signaling to the brain regarding breathing includes *1*) chemoreception by the peripheral and central chemoreceptors of arterial $P_{O_2}$, pH, and $P_{CO_2}$ and *2*) afferent signaling from the lungs, respiratory muscles, and chest wall regarding muscle effort, depth of breathing, lung stretching, and inflammation to the brain stem respiratory control center and its "corollary projection" to higher cortical centers such as the amygdala and anterior insular cortex, in which the conscious sensation of breathing resides (63). In addition, factors such as fever, anxiety, sympathetic nervous system activation, and increased metabolism contribute to ventilation and dyspnea perception. In focusing on silent hypoxemia, we emphasize that only a minority of patients seem to demonstrate the phenomenon and that it is generally shown early in their hospital presentation before deterioration to the point of needing mechanical ventilation. At this later stage, they can be extremely dyspneic for many reasons and require considerable narcotic dosing (64), as do many patients with ARDS.

### Reasons and Evidence for a Possible Unique Difference in Ventilatory Control and Dyspnea Perception in COVID-19 Lung Injury

As postulated above for HPV, if SARS-CoV-2 has a direct effect on peripheral oxygen sensing and response (a possibility given the presence of angiotensin-converting enzyme 2 receptors in the carotid body [65] and elsewhere in the central nervous system [CNS] [66]), then a direct, virally mediated effect at the level of the carotid bodies could potentially limit the ventilatory response to hypoxia and could decrease or abolish the sense of dyspnea

within the midbrain and higher cortical sensory areas. Other coronaviruses have been shown in animal models to affect medullary brain stem nuclei involved in respiration via the transmission of virus directly along afferent nerves arising in the lung, nasopharynx, and other peripheral mechanoreceptors and chemoreceptors (67). Recent autopsy findings in patients with COVID-19 have shown evidence for both SARS-CoV-2 RNA and protein in many areas of the brain stem and cortex that are often but not always associated with neuropathological changes (68). Thus, it remains possible that a neuropathic effect of the virus explains why some patients have little dyspnea despite their hypoxemia and lung inflammation.

### Reasons and Evidence against a Unique Difference in Ventilatory Control and Dyspnea Perception in COVID-19 Lung Injury

Normal variations within the population in ventilatory control, both in health and after acute lung injury, may better explain reduced or absent dyspnea in some patients with severe hypoxemic COVID-19 lung injury. Factors that likely contribute are better-than-expected lung compliance (equating to a decrease in the work of breathing) and hypocapnia that blunts the perception of dyspnea. In addition, some patients may have intrinsically blunted nervous system responses to hypoxia and hypoxemia. Signaling from the peripheral and central chemoreceptors in response to changes in arterial $P_{CO_2}$, pH and $P_{O_2}$, like that of HPV (49), varies 5-fold to 10-fold among healthy individuals (69, 70). Older patients and patients with diabetes have blunted hypoxic responses, and these two high-risk groups may thus experience less dyspnea when very hypoxemic; these patients are overly represented in COVID-19 lung injury (6). Furthermore, like the intraindividual variability of ventilatory responses to hypoxia, the symptomatic threshold for dyspnea onset during hypoxemia has high variability, with an observed threshold range of end-tidal $P_{O_2}$ from 35 to 60 mm Hg in healthy subjects with eucapnia maintained at fixed ventilation (71). It has not, however, been demonstrated that the same threshold for the dyspnea perception and range of variability applies to patients with inflammatory lung conditions.

## How Dangerous Is the State of Silent Hypoxemia in Patients with COVID-19?

Importantly, silent hypoxemia in COVID-19 should not be compared with states of chronic stable hypoxemia, such as high-altitude residence or congenital cardiac disease. Despite a decreased arterial oxygen content, these individuals develop compensations that allow adequate $O_2$ delivery and use, including polycythemia, higher $\dot{Q}$, greater gas exchange efficiency in the lungs and tissues, and more efficient oxygen use at the cellular level. These adaptations, some driven by HIF (hypoxia-inducible factor)–mediated gene upregulation, take considerably more time to evolve than the few days that patients are ill with COVID-19. In addition, it is unknown how these responses might be dampened or impaired by ongoing infection and inflammation in COVID-19.

Relatively asymptomatic patients with COVID-19 and with hypoxemia can have a high rate of rapid respiratory decompensation and greater mortality (72). However, it is unknown whether hypoxemia itself, in conjunction with systemic inflammation in COVID-19, contributes to further lung damage via an exacerbation of local inflammatory injury, as shown in nonventilated lung regions and other organs in non–COVID-19 disease (73). In addition, it is unknown to what extent hypoxemia contributes to microvascular insults and hypercoagulability that are likely playing a role in the high degree of other organ impairments in COVID-19 (74). Lastly, compensatory hyperventilation is not without risks; increased stress on less compliant lung regions with large tidal-volume efforts could contribute to further lung injury, a process known as patient self-inflicted lung injury (75).

## Proposals for Future Research

We propose further work to advance our pathophysiological understanding of COVID-19 lung injury, as clinical circumstances safely allow. These include more invasive measurements, including MIGET for $\dot{V}_A/\dot{Q}$ analysis and PA catheter–based assessment of pulmonary hemodynamics. Imaging to quantitate areas of abnormal and normal lung with correlation to compliance, pulmonary hemodynamics, and gas exchange will provide valuable insights. Key studies to establish a

better understanding of silent hypoxemia include the following:

1. Greater understanding of silent hypoxemia will be aided by future case reports or series containing more comprehensive data, including arterial blood gas and saturation values, respiratory rates, dyspnea scoring such as with the Borg scale, objective work-of-breathing assessments (76), CT imaging with quantitation of the extent of normal lung (GGOs and consolidations), preintubation compliance measurements, and standard ventilator data. Furthermore, physicians should report cases of silent hypoxemia in patients without COVID-19 to establish whether this phenomenon is truly unique in COVID-19.

2. Determining whether GGOs on CT images are areas associated with pulmonary angiopathy and thus with possibly having better compliance than GGOs associated with alveolar filling might involve inspiratory and expiratory CT scanning and assessment of volume changes as a surrogate for local compliance and directed lung biopsies.

3. Testing the strength of HPV in relation to the magnitude of hypoxemia and extent of radiographic imaging abnormalities might entail echocardiography in survivors of COVID-19 and their relatives to determine whether their greater hypoxemia was due to intrinsically blunted (and perhaps genetically determined) HPV. Testing whether the strength of hypoxic ventilatory response and dyspnea perception in survivors of COVID-19 and relatives to determine whether their greater hypoxemia was due to inherently diminished ventilatory responses or to a transient viral effect on chemosensitivity and CNS response should also be conducted.

4. Animal models of SARS-CoV-2 infection may also help to determine whether there is a direct contribution of the virus to altered HPV. This would allow more substantial studies, including short-duration inspired hypoxia with perfusion imaging or direct catheter assessment of intrinsic pulmonary vascular responses, as well as responses to vasoactive agents. These same experiments might test whether early virus infection alters ventilatory responses with the ability to isolate portions of the neural circuitry involved in ventilatory control.

## Conclusions

In conclusion, the pathophysiology of silent hypoxemia in COVID-19 lung injury remains inadequately explained. This uncommon presentation, never before reported in ARDS, may simply reflect individuals whose pattern of lung injury leads to a decrease in the work of breathing (less reduction in compliance) or whose unique combination of physiological responses maximizes hypoxemia (low HPV) while blunting the ventilatory response (low hypoxic ventilatory response) and dyspnea for any degree of lung injury. However, much remains to be learned about possible direct viral effects in the peripheral nervous system, CNS, and pulmonary vasculature in contributing to the above effects. A better understanding of the discordance among the extents of hypoxemia, dyspnea, lung compliance, and radiographic abnormality will be required before we can establish whether these manifestations are indeed a unique pathophysiological consequence of SARS-CoV-2 infection rather than a consequence of individual variability in the normal spectrum of pulmonary vascular and neural hypoxic sensitivities and responses.

Whatever the ultimate answer, patients with silent hypoxemia have a high risk for rapid deterioration. Thus, we believe terms such as "happy hypoxemia or hypoxia" should be abandoned to deter any complacency and deviation from well-proven and effective ventilatory and oxygenation support strategies in ARDS (77). Despite possible physiological explanations for silent hypoxemia, this state of relative repose does not preclude ongoing lung injury and systemic inflammation that can lead to respiratory failure despite close monitoring and supportive care. ∎

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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